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Editorial Comment

Antiarrhythmic Treatment and Myocardial Infarction*

EDMUND C. KEUNG, MD
San Francisco, California

Antiarrhythmic treatment of asymptomatic ventricular arrhythmias. The prognostic significance of ventricular premature depolarizations in patients who survive acute myocardial infarction is well established (1,2). Logic suggests that patient survival would be improved by eliminating these markers for cardiac mortality. The common practice of treating asymptomatic ventricular arrhythmias with antiarrhythmic agents in postmyocardial infarction patients had been based on the presumptive positive correlation between arrhythmia suppression and improved survival. However, whether elimination of ventricular arrhythmias leads to improved survival remains to be defined. For example, in 1983 Furberg (3) examined six randomized controlled long-term (4 to 24 month follow-up) trials of antiarrhythmic therapy with phenytoin, tocainide, mexiletine and aprindine in patients with myocardial infarction and concluded that, despite moderate to substantial suppression of ventricular ectopic activity, there were no statistical differences in total mortality between control and treatment groups. In the IMPACT study (4) there were no statistical differences in mortality between mexiletine and placebo treatment groups. Another study (5) failed to demonstrate a reduction in 1 year mortality with prophylactic antiarrhythmic treatment of high risk survivors of myocardial infarction. Although in general these studies did not demonstrate a significant effect, there were suggestions that antiarrhythmic drug treatment may actually have an adverse effect on survival in this patient population. Indeed, more recently, Hine et al. (6) demonstrated with meta-analysis a statistically significant *increase* in mortality in patients who received antiarrhythmic treatment as compared with control groups.

The CAST study. Despite a lack of convincing data to support a positive outcome with antiarrhythmic treatment in patients with history of myocardial infarction, many physicians have continued to pursue suppression of ventricular arrhythmias as a therapeutic goal in such patients. In one study (7), 52% to 73% of the cardiologists surveyed indicated that they would treat ventricular arrhythmias in asymptomatic patients who had had a recent myocardial infarction (7). In another study (8), 41% and 79% of the cardiologists interviewed would empirically treat asymptomatic ventricular premature depolarizations and nonsustained ventricular tachycardia, respectively. However, the practice of treating asymptomatic ventricular arrhythmias in patients with previous myocardial infarction was seriously questioned when the results of the Cardiac Arrhythmia Suppression Trial (CAST) were published in 1989 (9).

CAST is a prospective, randomized, placebo-controlled, double-blind study to test the hypothesis that suppression of ventricular arrhythmias reduces arrhythmic death in patients with moderate left ventricular dysfunction after myocardial infarction. Two type IC antiarrhythmic drugs, encainide and flecainide, and a phenothiazine derivative, moricizine (ethmozin), were selected for the active treatment arm. After 10 months of treatment, the patients treated with encainide and flecainide had a significantly higher incidence of death from arrhythmias and nonfatal cardiac arrest (4.5%) than did patients treated with placebo (1.2%), and the treatment arm involving encainide and flecainide was therefore discontinued. The CAST results have been the subject of much discussion. The adverse outcomes associated with encainide and flecainide understandably have been extrapolated to other type IC and even type IA and IB sodium channel-blocking agents. More important, the CAST results drastically altered much of our treatment approach to asymptomatic ventricular arrhythmias. The previous approach of "intention to treat" has been largely replaced by benign neglect in the management of ventricular arrhythmias in this group of patients.

The present study. In this respect the findings of Burkart et al. (10) in the current issue of the Journal are intriguing and provocative. In a prospective, randomized, open label study the incidence rates of total mortality, sudden death and life-threatening ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) were significantly lower in patients with moderate left ventricular dysfunction empirically treated with 200 mg of amiodarone daily immediately after myocardial infarction compared with rates in a placebo control group. The patients in the three study arms (individual treatment, amiodarone and control) were well matched with regard to left ventricular ejection fraction and severity of ventricular arrhythmias. Patient characteristics were comparable with those in the CAST study. One major difference in the study design is the timing of recruitment of patients with respect to the occurrence of myocardial infarc-

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From the Cardiology Section, Veterans Affairs Medical Center, San Francisco, California and the Department of Medicine, University of California, San Francisco, San Francisco, California.

Address for reprints: Edmund C. Keung, MD, Cardiology Section (111C), Veterans Affairs Medical Center, 4150 Clement Street, San Francisco, California 94121.

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tion. In the CAST study, patients were recruited 6 days to 2 years after myocardial infarction to begin the open label titration phase of the study. Moreover, only patients with arrhythmias successfully suppressed by encainide, flecainide or moricizine were randomized in the placebo-controlled trial.

The relatively long interval between occurrence of myocardial infarction and the double-blind placebo-controlled phase in the CAST study may well have contributed to the very low incidence of sudden death (1.2%) and total mortality (3.0%) in the placebo group (11) because most deaths among survivors of acute myocardial infarction occur within the first 6 months (12). The selection of patients who responded to antiarrhythmic drug treatment may have yielded a lower risk group compared with patients with ventricular arrhythmias unresponsive to drug treatment (13,14). In the present study, patients with acute myocardial infarction who met the entry criteria were immediately randomized to one of the three treatment arms before discharge from the hospital. Unlike the CAST study, in this study there was no open titration phase to select treatment responders. Thus, not unexpectedly, the total mortality rate of 13% in the control group is much higher than that in the CAST study but more comparable to previously reported values (12).

Why is amiodarone effective? A plausible and obvious explanation for the favorable outcome of amiodarone treatment is that this agent is effective in preventing sudden death resulting from ventricular tachycardia and fibrillation. This is suggested by a significant difference in the incidence of life-threatening arrhythmia events between the control and the amiodarone group. In fact, amiodarone is perhaps the most effective agent currently available (15) for treatment of sustained ventricular tachycardia and ventricular fibrillation. As indicated by Burkart et al. (10), amiodarone has an antifibrillatory effect. The cellular mechanism of its antiarrhythmic action is not clear. Amiodarone has unique electrophysiologic properties that are not shared by other antiarrhythmic agents. It is classified as a type 3 agent because it prolongs cardiac action potential duration (16). Prolongation of action potential is probably due to its blocking effect on the inward rectifying (17) and the delayed rectifying potassium channels (18). It also exhibits use-dependent block of the cardiac sodium channel (19,20). In this respect, it can be categorized as a type 1 antiarrhythmic agent. It preferentially inhibits cardiac sodium channels in the inactivated state. Thus, amiodarone slows conduction in Purkinje fibers and myocardial tissues, especially in rapidly beating partially depolarized ischemic tissues. Moreover, it has been shown to inhibit adenosine triphosphate (ATP)-sensitive potassium channel activity (21), which may play a significant role in modulating arrhythmogenesis during myocardial ischemia (22).

In addition to its direct blocking effects on various cardiac channels, amiodarone also exhibits beta-adrenergic blocking effects (23,24). Beta-adrenergic antagonists have been shown unequivocally to reduce the incidence of sudden death in survivors of myocardial infarction (25). As pointed out by Burkart et al. (10), as a result of its beta-blocking properties, amiodarone may have a favorable effect on survival beyond a direct electrophysiologic mechanism.

An interesting apparent difference in the patient characteristics in the present study is worth mentioning. The 32% incidence rate of anterior myocardial infarction in the amiodarone treatment group was lower than the rate (44%) in the control and individual treatment groups. Anterior myocardial infarction has been demonstrated to have a higher mortality rate than inferior myocardial infarction even after correction for infarct size (26,27). One has to wonder if the apparent lower incidence of anterior myocardial infarction affected the outcome in the amiodarone treatment group.

Implications. Because of the serious side effects of amiodarone (28), its potential benefit in reducing arrhythmic mortality has to be carefully examined in a much larger group of patients. The most worrisome adverse effect is pulmonary fibrosis, which has been reported in 1% to 13% of patients treated with amiodarone and has a mortality rate of 10% to 23% (15,28). This rate may be 11% to 15% in patients treated for >1 year. There is also evidence for increased frequency of pulmonary fibrosis with time of treatment and with cumulative dose (28). Burkart et al. (10) did not observe any overt pulmonary toxicity during 1 year of amiodarone treatment. However, because no pulmonary function tests were performed, the possibility of pulmonary dysfunction such as reduced vital capacity and diffusion capacity cannot be ruled out. In general, lowering the daily dose of amiodarone reduces the incidence of major adverse effects. However, as discussed previously, long-term treatment even at lower doses may result in unacceptable adverse morbidity and mortality that may negate the favorable effect of amiodarone on survival through reduction in sudden death and life-threatening ventricular arrhythmias. A daily dose of 200 mg of amiodarone has been shown to be effective in treating life-threatening ventricular arrhythmias. It remains to be seen if lower doses would maintain the same beneficial effect while reducing the incidence of adverse events.

In view of the findings of CAST, the present study by Burkart et al. (10) is intriguing and provocative. The beneficial results observed in the amiodarone treatment group are encouraging and warrant further investigation. This report clearly serves as a pilot study for a large scale prospective multicenter randomized placebo-controlled trial.

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